EVALUATING THE POTENTIAL NEGATIVE EFFECTS OF SCHOOL-BASED PREVENTION PROGRAMS AIMING TO REDUCE ALCOHOL AND DRUG MISUSE IN ADOLESCENTS: A SYSTEMATIC REVIEW OF RESEARCH ARTICLES PRIOR TO 2013

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Evaluating the potential negative effects of school-based prevention programs aiming to reduce alcohol and drug misuse in adolescents: A systematic review of research articles prior to 2013.

Negative effects of prevention programs

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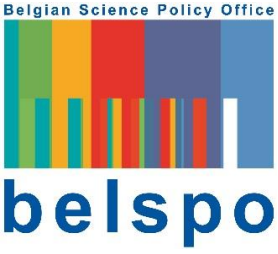

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Abstract

Issues: Reviews of alcohol and drug prevention programs commonly focus on positive effects, whilst disregarding possible iatrogenic effects. Our objective was to summarize evidence on iatrogenic effects of alcohol and drug prevention programs targeting adolescents. We systematically investigated the nature of these effects, the number of iatrogenic effects reported on, the sort of impact they have (e.g. in terms of severity) and the type of programs associated with iatrogenic effects.

Approach: On January 2013, we searched the Cochrane Central Register of Controlled Trials, Medline, PsycINFO, Web of Science, Eric, Scirus and we actively searched for grey literature via Google Scholar and OpenGrey. Included were (quasi) RCTs that evaluated the effectiveness of school-based alcohol and drug prevention programs for adolescents. Ninety-three articles were eligible for inclusion and were screened for potential iatrogenic effects.

Key findings: Ten articles reported on iatrogenic effects, which were predominantly found on substance use outcomes. The quality of these articles was assessed and a meta-analysis was not possible due to the heterogeneity in interventions and outcome measures. An increase in substance use was found in 5 out of 7 RCTs and in 1 quasi RCT. The magnitude of the iatrogenic effects found was not always clear due to the outcome measures used.

Implications: Iatrogenic effects were assessed in a limited number of studies. In future studies on prevention programs the number, nature and impact of iatrogenic effects should standardly be assessed and reported. It allows us to detect potential problem areas in the conceptualization of prevention programs.

Keywords: alcohol drinking, substance abuse, prevention, review literature, adverse effects

Introduction

Alcohol and drug misuse pose a problem to society and is related to several adverse outcomes. According to the World Health Organization [1], alcohol consumption results in approximately 3.3 million deaths each year and harmful use of alcohol is one of the world's leading risk factors for morbidity, disability and mortality. Alcohol and drug related problems place an enormous financial burden on today's modern society [2-3]. On a societal level, alcohol and drug misuse are related to crime [4], health problems [6] and psychological problems [7].

Adolescents are a particularly vulnerable population when it comes to the deleterious effects of alcohol and drug use. Research has shown that experimentation is relatively common among adolescents [7] and that drug dependency usually starts in adolescence [8-10]. In addition, the 2011 European School Survey Project on Alcohol and Other Drugs Report also states that alcohol- and drug use is quite common during adolescence [11]. Thirty-nine per cent of adolescents, with a mean age of 15.8 years, drank heavily during the past month, 17 per cent has used marihuana at least once and 6 per cent has used another illicit drug other than marihuana at least once.

Drug and alcohol misuse during adolescence is risky, because it impacts on critical stages of brain development [12-13]. It can modify the structure and function of the brain, which leads to interference with brain development and higher risk of addiction [14]. Early drug use has also been associated with higher rates of mental health problems. This further increases the likelihood of regular and problematic use [15].

Other specific risk factors that put adolescents at risk for substance use include environmental and cultural factors. This is supported by findings of multiple studies [16-18] identifying both protective and risk factors for substance use initiation in adolescence. The importance and influence of school, for example, is reflected in the finding that there's a negative relationship between the lack of school attachment and commitment and the development of substance abuse [19]. High academic achievement seems to be the most important school-related protection factor [20-22]. The findings from previous studies illustrate that the future of adolescents and their position in society can become severely compromised as a consequence of alcohol and drug use. Therefore, it is crucially important to invest in prevention initiatives.

A vast amount of these programs are school-based. Examples of such programs include Project ALERT [23], keepin' it REAL [24], Project Towards No Drug Abuse [25] and Unplugged [26]. A substantial number of these programs yield positive effects. However,

according to a review conducted by Foxcroft and Tsertsvadze's [27] some generate no effect or even a harmful effect. According to Werch and Owen [28], negative outcomes are rarely detailed in evaluation research on substance use prevention interventions, which is designed primarily to examine positive program effects.

In 2002 Werch and Owen [28] systematically analyzed published studies evaluating substance use prevention programs to determine whether iatrogenic effects (i.e. any negative, harmful effect that occurs as a result of participating in a prevention program) occurred. For their review, Werch and Owen focused on primary or secondary prevention programs that targeted youth or young adults. Iatrogenic effects were found and subsequently, they examined the types of harmful effects and under what circumstances the effects occurred. The majority of iatrogenic effects were behavioral effects consisting primarily of increases in consumption, especially alcohol use. Based on their findings, Werch and Owen also suggested that addressing multiple substances could possibly increase the probability of harmful substance use over single substance prevention programs.

Objectives:

Although there is a general awareness about the importance of considering iatrogenic effects of programs, they have not been a focal point in many reviews on drug and alcohol misuse. This systematic review project aims to fill in this gap, by focusing on the potential iatrogenic effects of school-based programs to prevent drug and alcohol use in adolescents and summarizing the available evidence on the topic. It builds on the insights generated by Werch and Owen [28] and provides a substantial update of their review. Our primary goal is to determine if and how many iatrogenic effects are reported. Secondly, we aim to investigate the nature and impact of these iatrogenic effects, and in which type of programs such iatrogenic effects are likely to occur. Only randomized and quasi-randomized clinical trials (RCT and qRCT) were considered where the control condition was a standard curriculum.

Methods

We adopted the methodological outline for systematic reviews described in the 'Cochrane Handbook for Systematic Reviews of Interventions' [29] and opted for a narrative synthesis as the overall design for the review. The review protocol, which was developed prior to conducting the systematic review, is available on request from the authors.

Inclusion and exclusion criteria

Our population of interest were adolescents, typically aged 12 to 18 years. The types of studies included were RCTs and qRCTs evaluating drug and alcohol prevention programs that are implemented in a school setting. Prevention programs organized as an extracurricular activity were excluded. Programs that focused solely on smoking prevention were also excluded since we perceived this to be a different field of research and our review's main focus was on mind-altering substances. A drug and alcohol prevention program was defined as an educational, informative program with the objective to prevent or decrease the use of alcohol and drugs. Information campaigns and skills training were included. Prevention programs that also included therapy sessions (therapy was defined as being a treatment on a psychological level with the goal of altering/adjusting the thoughts or behavior of the adolescent with regard to alcohol- or drug use) were excluded. We consider therapy to be outside of the scope of school-based interventions. Furthermore, these programs are primarily aimed at problem youth. Helping these youngsters therapeutically is not one of the main tasks of the school. In addition, to be included the control condition of these studies had to be a standard curriculum. For types of outcome measures we considered all iatrogenic effects. Examples include increase of use, positive attitude towards drugs, problem behavior, etcetera. Studies written in languages other than English or Dutch were excluded. Studies with a follow-up period that exceeded one year were also excluded as we focused on direct and immediate iatrogenic effects. In addition, we expected that the longer the follow-up period, the more likely results are affected by other factors than the prevention program.

Search methods for identification of studies

In January 2013, we searched the following databases: the Cochrane Central Register of Controlled Trials (including the Cochrane Drugs and Alcohol groups specialized register), Medline through PubMed (freely accessible at: http://www.ncbi.nlm.nih.gov/pubmed/), PsycINFO through OvidSP, Web of Science, Eric through OvidSP and Scirus (freely accessible at: http://www.scirus.com/). Additionally, the following sources of grey literature were searched: http://scholar.google.be/ and http://www.opengrey.eu/search/. We developed a search strategy based on the categories described in the inclusion criteria. The important concepts were: adolescent, high school, prevention, alcohol and drugs. For Medline we added the Cochrane Highly Sensitive filter for identifying RCTs (2008 revision) from the Cochrane Collaboration [30], which consists out of a methodological filter and a filter for excluding animal studies. The strategy developed to search the Medline database can be found in the

supplementary file (table S1) and this search strategy was adapted for every single database. All retrieved studies were downloaded in an EndNote database, version X6.01 [31].

Screening and analysis

Selection of studies

The selection of studies consisted of two phases. First, titles and abstracts of the studies were screened to determine whether or not they were eligible for inclusion. Subsequently, the full-text articles of potentially relevant studies were retrieved. When a study could not be found, we emailed the original authors with the request to provide us with a copy. The full-text articles were then examined in order to decide whether or not they met the inclusion criteria. One reviewer screened all the studies (BDC). In case of doubt, the potential in- or exclusion of the study was discussed with a second reviewer (GEB). Discrepancies between the reviewers were solved by involving a third reviewer (KH).

Quality assessment

Methodological quality of the studies was assessed through use of the Quality Assessment Tool for Quantitative Studies, which evaluates both internal and external validity [32]. We considered the instrument developed by the Effective Public Health Practice Project (EPHPP, McMaster University, Ontario, Canada) as useful for assessing studies of public health and health promotion interventions, since it has been used in other studies on health promotion as well [33-34].

In order to rate the quality of a certain study, we took its global score which is determined by the scores on the components selection bias, study design, confounders, blinding, data collection, methods, withdrawals and dropouts. The rating of these components consists out of a three-point scale: weak, moderate or strong. Depending on the overall number of weak ratings, the global score is strong (no weak ratings), moderate (one weak rating) or weak (two or more weak ratings). More information on the rating of the components can be found in the supplementary file (table S2). The Quality Assessment Tool for Quantitative Studies Dictionary [35] provides guidelines for the rating of the components and their items.

The quality assessment of the included studies aimed to gather information about the study quality and hence how much trust we could have in the results of the included studies. Additionally, this provided us with a baseline measure for the quality. Studies were not excluded based on methodological quality. Our review covered studies from a wider period of

time and current criteria were most likely not yet applicable to older studies conducted. The quality assessment was performed by BDC and verified by GEB.

Data extraction and analysis

Characteristics of the selected studies were extracted using a data extraction form partially based on the "Data collection form for intervention reviews for RCTs and non-RCTs" of the Cochrane Collaboration [36] and partially on the data extraction form used in the review of Werch and Owen [28].

Due to poor reporting and different outcome measures used, meta-analysis with statistical pooling of data was not possible. Even though all studies made use of self-reported measures, the included studies used different questionnaires. Details on the type of questionnaires used were scarce or absent. Consequently, we were not able to combine the estimates and we therefore chose to summarize the findings in a tabular form, accompanied by a narrative that provides more details.

Results

Results search strategy

The results of the search strategy are presented in figure 1. We screened 93 articles in full text. Of the 93 articles, only 5 explicitly stated that they evaluated the programs for iatrogenic effects and of these, 3 did not find any iatrogenic effects. Ten articles, reporting on 8 unique studies, reported iatrogenic effects and were included for analysis. The articles of Clark et al. [37] and Ringwalt et al. [38] and the articles of Hallfors et al. [39] and Cho et al. [40] reported on the same dataset.

Characteristics of included studies

The characteristics of the studies are described below and can also be found in table 1. Detailed information can be found in the online supplementary file (see table S3).

Intervention: The included studies evaluated 7 different drug and/or alcohol prevention programs: a cognitive, behavioral approach to substance abuse, Life Skills Training and Timewise combined, Project ALERT, Reconnecting Youth, Resistance skills training and normative education (separate and combined), a school-based alcohol education intervention, and Project Towards No Drug Abuse (TND) and TND network.

Study design: One study was a standard RCT and six were cluster RCTs. The remaining study had a quasi-experimental age-cohort design.

Sample: The number of participants ranged from 715 to 7,742 and every study had a relatively equal distribution with regard to gender. Ethnicity was not always equally distributed. The youngest participants were sixth grade students and the oldest were eleventh grade students. Seven studies took place in the United States of America and one in Germany.

Providers: The majority of programs were delivered by teachers, whom received training before implementation. In other studies, the intervention was delivered by project staff or adults who were trained. Three studies evaluated programs that were (partially) led by peers (fellow students).

Content of intervention: In the majority of programs, students were taught skills to refrain from drug and/or alcohol use. Most, if not all, programs actively engaged students in their learning process.

Important characteristics of programs: The program or part of the program was delivered by regular classroom teachers in 5 studies [37-40, 42-44]. In 3 studies, there was also a peer-led or –assisted experimental condition. In 2 studies this condition had iatrogenic effects [41, 45]. Moreover, Valente et al. [41] found that substance use increased as peer use increased.

Six of the 7 programs addressed multiple substances. Four programs incorporated social skills training and 4 programs focused on the consequences of substance use. Four programs focused on altering the normative beliefs/expectations of drug use. In addition, 5 of the 7 different programs incorporated skills/methods training to teach students how to resist peer pressure. Concerning the content of the programs, each intervention had a different focus and consisted out of distinct lessons and activities (e.g. group sessions).

In 3 programs, the program also had booster sessions. Botvin et al. [42] found that the teacher-led version of the program with booster sessions produced iatrogenic effects. Iatrogenic effects for booster sessions were found by Ringwalt et al. [38] when teachers were trained in person.

Outcomes: All studies had self-reported outcome measures, which were primarily substance use outcomes and mediating outcomes.

Methodological quality of studies

The results of the quality assessment are presented in Table 2. More detailed results of the quality assessment are included in the online supplementary file (see table S4).

Selection bias: Four studies selected participants who were very likely to be representative of the target population. Concerning the percentage of selected participants whom agreed to participate, 1 study had an 80 – 100 % agreement rate, 2 studies had a 60 – 79 % agreement rate and 5 studies gave no information about the agreement rate.

Study design and Confounders: Seven studies were classified as an RCT. Of these, 6 did not describe their method of randomization. Further, 2 studies did not give enough information to determine whether or not there were important differences between groups prior to the intervention. In 3 studies, there were important differences between groups prior to the intervention and in these 3 studies, most (80 – 100 %) relevant confounders were controlled for.

Blinding and Data collection methods: Outcome assessors were not aware of the intervention or exposure status of participants in 5 studies. None of the studies reported whether or not the study participants were aware of the research question. Two studies used data collection tools which were shown to be valid and 3 studies used data collection tools which were shown to be reliable.

Withdrawals and dropouts: Three studies reported on withdrawals and dropouts in terms of numbers and reasons per group, 4 studies had a percentage of participants completing the study within the range of 80 – 100 % and 4 studies within the range of 60 – 79%.

Global rating: One study had a global rating of strong, 1 study had a global rating of moderate and 6 studies had a global rating of weak methodological quality.

Results on iatrogenic effects

The results are summarized in table 3. A more detailed description of the results and supplementary information about the included studies can be found in the online supplementary file (see table S5).

Number of iatrogenic effects

Overall, 25 significant iatrogenic effects were reported. Of these, 14 were on substance use outcomes (56%), which consisted out of an indirect and direct increase in substance use. Predominantly affected was the use of marijuana and alcohol.

Substance use outcomes:

Alcohol: Four studies reported an increased alcohol use after the experimental intervention. Students in the experimental intervention increased their alcohol use at post-test

[37-38, 42]. Additionally, there were more students who drank alcohol at post-test in the experimental intervention [42, 46].

Marijuana: Five studies reported direct and indirect increased marijuana use. Hansen and Graham [46] reported that one of the programs was inferior to the control condition in preventing the onset of marijuana use, which we consider to be an indirect increase of marijuana use. Additionally, 4 studies reported a direct increase in marijuana use in the experimental intervention [37-38, 41, 45].

Other substances: Three studies reported increased use of other substances. Inhalant use [38], cocaine use [41], and the use of multiple substances [41, 43] was increased in the experimental intervention.

Mediating outcomes: Eight (32%) iatrogenic effects were on mediating outcomes, more specifically on attitudinal and behavioral outcome measures.

Attitudinal outcomes: Participants in the experimental intervention had more positive attitudes towards alcohol [42, 44] and marijuana [42]. In addition, 1 study [45] reported that expectations of future marijuana use were higher among participants in the experimental intervention.

Behavioral outcomes: The control group showed better drug refusal skills than the intervention group [38]. In addition, iatrogenic outcomes were found on conventional peer bonding, high-risk peer bonding and prosocial weekend activities [39-40]. Conventional peer bonding refers to the bonding of students with peers that are not commonly affiliated with substance use (e.g. peers that spend lots of time with their families). Contrary to conventional peer bonding, high-risk peer bonding denotes peers that do use substances and show other problem behaviors. Prosocial weekend activities were activities such as doing homework.

Other outcome measures: Three (12%) iatrogenic effects were on other outcome measures. That is, anger was higher and school connectedness and GPA (Grade Point Average) were lower in the experimental group [39-40].

Severity and impact of iatrogenic effect

The majority of studies gave little information on the severity and impact of the iatrogenic effects (i.e. not all the estimates contained information on the magnitude of the iatrogenic

effect). Therefore, iatrogenic effects of at least a moderate magnitude (i.e. if an effect size was given and if it was indicative of at least a moderate iatrogenic effect) are summarized below.

Substance use outcomes:

Alcohol: There was a substantial difference between the proportion of drinkers in the control group and the teacher booster group on the monthly measure (proportion control group = .38; proportion teacher booster group = .55; $p < 0.0001$) and, in a lesser extent, the weekly measure (proportion control group = .20; proportion teacher booster group = .33; $p < 0.001$) [42].

Marijuana: The teen-assisted version had a 149% greater increase in the odds of past year marijuana use for students receiving that version of the program, relative to the increase between the pretest and posttests for students in the control condition [45].

Mediating outcomes:

Behavioral outcomes: There was a clear difference between the experimental group and the control group on high-risk peer bonding (adjusted means 1.62, *SE* = 0.04, and 1.82, *SE*= 0.06, for control and experimental group respectively; $p = 0.01$) and prosocial weekend activities (adjusted mean control group = 4.23, *SE* = 0.10; adjusted mean experimental group = 3.84, *SE* = 0.15; $p = 0.03$) [39-40].

Other outcomes:

Anger: There was a difference on anger (adjusted mean control group = 1.22, *SE* = 0.03; adjusted mean experimental group = 1.39, *SE* = 0.05; p = 0.01) [39-40].

Programs:

In the studies that reported iatrogenic effects there were certain common elements in the prevention programs such as: a) the experimental condition was given or assisted by peers, b) addressing multiple substances, c) focusing on the consequences of substance use or d) additional booster sessions.

Discussion

Alcohol and drug prevention programs are developed and delivered to yield positive effects. While it has been proven that these have desired effects, much less is known about potential undesirable iatrogenic effects. The primary objective of this systematic review was to determine whether these programs may also produce iatrogenic effects. We found that prevention programs may produce iatrogenic effects. However, our review cannot provide firm

conclusions on the type of prevention programs that should be re-designed or abandoned, due to poor reporting and heterogeneity between the interventions and outcome measures in the included studies.

Our secondary objective was to investigate the nature of these iatrogenic effects, how many have been reported and the impact they have on the target group. We found that iatrogenic effects occurred in substance use outcomes, in mediating outcomes and in other outcomes. Substance use outcomes were predominantly affected (56 %) and consisted out of an indirect and direct increase in substance use. Also affected, but to a lesser extent, were the mediating outcomes (32 %). Twenty-five significant iatrogenic effects were reported in total. However, only a few of them could be interpreted to be meaningful due to the outcome measures used. Frequently, studies used multilevel modeling to present their results. This type of analysis is less informative on the magnitudes of these effects. In order to interpret the significance and consequences of the results, it is necessary to provide clarity on the magnitude. This was typically poorly reported in the included studies.

Our third objective was to investigate which programs are associated with these iatrogenic effects. The programs that generated iatrogenic effects may share some core characteristics, such as peer involvement, a focus on multiple substances, a focus on the consequences of substance use and booster sessions.

The iatrogenic effect found for programs given or assisted by peers could be attributed to deviancy training. Deviancy training is a process by which children receive subtle social support and rewards from their peers for aggressive or delinquent behavior [47]. As a result, problem behavior increases. This phenomenon was clearly observed in the study of Valente et al. [41]. It was found that the peer-led program accelerated peer influences and, as a consequence, substance use increased for students with a peer environment that supported substance use. In line with this finding, Dishion et al. [48] found that substance use increased in peer-group programs. A similar finding was found by Werch and Owen [28], who reported that a peer-group program leads to iatrogenic effects when high-risk youth are exposed to high-risk peers. Several systematic reviews found mixed evidence for peer-led programs, however [49-52].

Furthermore, programs targeting multiple substances may be associated with harmful effects. According to Werch and Owen [28], it is possible that addressing multiple substances reduce the perceived risk for substances viewed as less dangerous (e.g., alcohol or cigarettes) when compared to other types of drugs (e.g., cocaine or heroin). Werch and Owen [28] postulated that broader prevention programs could be more hazardous than focused programs

and this was supported by a study of Piper and colleagues [53]. However, we cannot conclude that addressing multiple substances causes iatrogenic effects since we have not been able to generate enough evidence on focused programs.

Four programs focused on the consequences of substance use and only one study [46] gave a more elaborate description on the content of the lessons. We therefore consider this study to be the best case, since the other studies did not provide any information on what they meant by focusing on the consequences of substance use.

Three programs also had booster sessions and in one study [42], the teacher-led version of the program with booster sessions showed an iatrogenic effect. The latter study was the only one that evaluated the version of the program with booster sessions. Adding booster sessions may possibly be harmful. In the study of Gmel et al. [54], adding booster sessions to the program resulted in an increase in substance use. Furthermore, in the systematic review of Soole et al. [52] on the effectiveness of school-based drug prevention programs in preventing illicit drug use, it was found that, in a number of instances, programs with booster sessions appeared to have an unintended negative impact on program effectiveness. This, however, does give definitive evidence that adding booster sessions produces iatrogenic effects.

Finally, there is evidence that some of the iatrogenic effects may be due to implementation failure or a type III error (i.e. effects due to unsuccessful implementation of the program) [55]. This could explain why the Reconnecting Youth intervention was found to be effective in the efficacy trial and was later found to be harmful in the effectiveness trial [39, 40]. Additional evidence was found in Ringwalt et al. [38], where the iatrogenic effect of the booster sessions depended on the mode of teacher training. Hence, poorly managed prevention programs may be more likely to introduce iatrogenic effects.

Limitations

The first limitation pertains to the generalizability of our findings to non-Western countries. The majority of included studies were located in the United States of America. Hence, replication is needed to determine whether or not we can generalize our findings to non-Western cultures. Second, there was a low level of overlap between programs, making it difficult to link an iatrogenic effect to a certain characteristic of the program. Third, most of the studies had a weak methodological quality. It should be noted, however, that 6 of 8 studies were older than 5 years and 2 of them even more than 10 years old. Therefore, it is not surprising that most studies were rated weak. Furthermore, alcohol and drug prevention interventions are complex

interventions considering that there are multiple uncontrollable variables. Hence, it could well be that the tools used are not appropriate for assessing their methodological quality. Fourth, we excluded studies with a follow-up longer than 1 year. There's a higher probability that follow-up measurements exceeding 1 year are affected by other factors than those of the intervention. Notwithstanding, it is likely that, by excluding these studies, we did not capture the full array of iatrogenic effects caused by alcohol and drug prevention programs. Fifth, only 10 articles of the 93 screened in full text reported on iatrogenic effects. One could argue that the iatrogenic effects found can be linked to a type I-error. This line of reasoning might not apply here, as the number of is possibly underestimated due to a publication bias for studies reporting negative results only or iatrogenic effects found but not being reported on. Also, the exclusion criteria for this review could possibly have resulted in a conservative estimate.

Implications and future research

In preventing substance use, we should be careful that we don't promote programs that exert iatrogenic effects. Even in programs that generally yield positive outcomes, there's a risk for a boomerang effect [56]. That is, the prevention programs do not produce the intended, positive effect. Instead, they produce an unintended, iatrogenic effect. The latter is also the case in large-scale prevention programs that claim to be effective although later research shows otherwise [57]. Prevention programs, certainly government funded programs and widespread interventions, should regularly be evaluated for their effectiveness. Researchers should also regularly update the effectiveness of these programs and pay special attention to possible iatrogenic effects. However, in order to find iatrogenic effects, one must search for them. In our review only 2 of the 10 included studies explicitly evaluated their program for possible iatrogenic effects and this is far too little to draw any firm conclusions. Possible reasons for the low number of studies with iatrogenic effects are publication bias as well as possible financial and professional consequences. It is reasonable to assume that investigators that receive funding for developing a prevention program are less inclined to report on the absence of positive effects and/or the presence of iatrogenic effects. In addition, the absence of a framework to systematically monitor and report adverse effects in drug prevention programs could also contribute to the low number of studies. To our knowledge, there are no clear definitions of iatrogenic effects caused by prevention programs and no structured assessment methods to capture these effects. Future research can aid by developing such a framework as well as a structured assessment method to measure iatrogenic effects caused by drug prevention programs which also takes the intermediate effect of the setting into account [55]. This could

possibly help in uncovering factors that explain why programs that previously were found to exert positive effects, can also exert iatrogenic effects. A commendable example from a different research domain can be found in the article of Linden [58] in which a model is proposed to find, classify and evaluate negative events in psychotherapy. It could be advantageous to have such a study design that focuses specifically on iatrogenic effects. This could be an important addition to evaluation research in that it exposes the weaknesses of an intervention that would otherwise never be uncovered. Future research can aid in the development of effective, non-harmful alcohol and drug prevention programs by examining the causes of potential iatrogenic outcomes identified. This review hopefully serves as an impetus for future research to examine which factors cause these harmful effects and to evaluate our findings in other contexts (e.g. peer deviancy training). In addition, it could be advantageous to work towards achieving consensus on the set of mediating variables of the initiation/continuation of substance use that should be considered by researchers. This would facilitate the statistical pooling of data, both of positive and harmful effects of programs.

Conclusion

Our main finding is that there are alcohol and drug prevention programs that produce iatrogenic effects. Iatrogenic effects manifest themselves in substance use outcomes, in mediating outcomes and in other outcomes. Substance use outcomes were predominantly affected and consisted out of an indirect and direct increase in substance use. The magnitude and severity of these iatrogenic effects was not always evident due to the outcome measures used which is important to assess the clinical relevance of these findings. In conclusion, future studies should evaluate iatrogenic effects as part of their assessment. We further welcome the input and effort of colleague researchers in conducting future updates of this review.

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Conflict of interest

None to declare.

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Tables

Table 1. Characteristics of studies

Study/Intervention (Refs) Design	Sample	Content of intervention/model	Providers	Outcomes
A cognitive-behavioral approach to substance abuse Botvin et al. (1990) Cluster RCT	1311 eighth grade students from 10 suburban New York junior high schools. N 1-yr follow-up= 998 (76%) Gender: 49% male; 51% female. Ethnicity: 80% white	Four interventions: (1) program implemented by older peers, (2) program implemented by teachers, (3) Booster sessions implemented by older peers, (4) Booster sessions implemented by teachers. The intervention in this study is a multi-component program focusing on the major social, psychological, cognitive, and attitudinal factors which appear to promote the use of tobacco, alcohol, and marijuana. The 20-session program, delivered in 7th grade, focuses on the consequences of substance use and its social acceptability, decision-making, resisting social influences to engage in substance use, self-directed behavior change, cognitive-behavioral techniques for coping with anxiety, communication skills, general interpersonal skills, and assertiveness. The booster curriculum, delivered in 8th grade was designed to reinforce the prevention program.	Peers (peer leaders from 10th, 11th and 12th grade) and regular classroom teachers. Both the peer leaders and teachers received a 4 hour training workshop, conducted by the members of the project staff. Peer leaders participated in a series of briefing sessions which provided them with more specific preparation for each upcoming session.	Self-reported smoking, drinking, and marijuana use behaviors, cognitive, attitudinal, and personality measures.
A school-based alcohol education intervention Morgenstern et al. (2008) Cluster RCT	1875 seventh grade students from thirty schools in Germany, Baseline: Gender: 51,8 % male; 48,2 % female Mean age: 13,0 years	The program consisted of four specified class units, a booklet for students and a parent booklet. The main message of the materials was 'no alcohol for minors' and the intervention focused on addressing social influences and enhancing motivation to avoid substance use. Each teaching unit had a standard structure that included a schedule, an overarching theme, the main objectives and a list of 'hands-on' materials. Instructions for working interactively were described for each teaching unit.	Teachers of 7th grade students implemented the intervention. Implementation teachers received a 3-hour workshop introducing the underlying concepts and materials for the intervention and demonstrating potential realizations in the class.	Self-reported alcohol use measures, alcohol-related knowledge, attitudes and intentions, and potential covariates.

The iatrogenic effects of the studies have been summarized in table 3.

Table 1. (continued)

Study/Intervention (Refs) Design	Sample	Content of intervention/model	Providers	Outcomes
Life Skills Training and Timewise combined Ferrer-Wreder et al. (2010) quasi-experimental age-cohort design	715 students from USA ranging in age from 11–16 years old (M = 12). Gender: 45% male; 54% female; 1% missing. Ethnicity: 64% Black; 32% ‘‘Other’’ ethnic identifier; 4% missing.	Life skills Training (LST): is a universal school-based drug prevention program and is grounded in social learning, communication, and problem behavior theories. LST consists of activities designed to help youth learn how to say no when tempted to engage in substance use and aims to help youth learn to make good decisions, set goals for themselves, and realize the impact of their behaviors Further, LST consists of activities aimed at improving general social skills. Other LST targets for change include identity development, problem solving or decision-making, interpersonal relationships, physical health maintenance, and correcting normative expectations about substance use. Taking Charge of Leisure Time (Timewise): is a universal school-based health promotion intervention that is designed to educate youth about how to use their leisure time in healthy ways. TimeWise focuses largely on health promotion rather than risk reduction. It specifically targets the reduction of drug use in leisure time by helping youth better understand the connection between their leisure time and development.	Teachers whom were trained in LST and Timewise. Teachers had a two-day on-site LST training by National Health Promotion Associates and a one-day on-site TimeWise training by the intervention’s developer.	Self-reported drug use, LST-related scales, Timewise-related scales and dosage.
Project ALERT Clark et al. (2011); Ringwalt et al. (2010) Cluster RCT[a]	7,742 sixth-grade students from 34 schools in USA, N 1-yr follow-up= 4940 (64%) Baseline: Gender: 49% male, 51% female Ethnicity[b]: 52% Caucasian; 16% African American; 27% Hispanic.	Project ALERT, a 2-year prevention program which targets cigarette, alcohol, marijuana, and inhalant use. 11 lessons are given during 6th grade and three during 7th grade. The lessons stress motivating nonuse, identifying internal and external pressures to use drugs and practicing skills to resist those pressures, and identifying the benefits of nonuse. Students in the control condition did not receive any evidence-based substance use prevention program nor did they receive project ALERT.	Instructors (69 teachers and two counselors) completed training, either online (n=43) or at an in-person workshop (n=28).	Self-reported use of cigarettes, alcohol, marijuana, and inhalants and self-reported intentions to use and number of times offered a substance.

Table 1. (continued)

Study/Intervention (Refs) Design	Sample	Content of intervention/model	Providers	Outcomes
Project ALERT St. Pierre et al. (2005) Cluster RCT	1,649 7th-grade students from eight middle schools in USA. Schools varied in socioeconomic level. N 1-yr follow-up = 1196 (72.5%) Gender: 50.5% male; 49,5% female Ethnicity: 81.4% Caucasian; .	The revised Project ALERT delivered contains 11 lessons offered weekly in 7th grade, and 3 lessons in 8th grade. The new lessons emphasize smoking cessation skills, consequences of alcohol misuse, alternatives to drinking, and consequences of inhalant use. The two experimental conditions consisted of an adult-led Project ALERT condition and an adult-led, teen-assisted Project ALERT condition.	Penn State Cooperative Extension (CE) Educators hired qualified adults in the community as adult program leaders. For classrooms in the adult-led teen-assisted condition, teen leaders assisted with program delivery for 5 of the 11 7th-grade lessons. These teen leaders participated in a 1-day training conducted by the researchers, CE Educators and adult program leaders.	Self-reported substance use, mediating variables for substance use, indicators of use and cognitive mediators.
Reconnecting Youth Hallfors et al. (2006) ; Cho et al. (2005) RCT	1370 high-risk 9th to 11th grade students, recruited from 9 high schools in the United States. Gender: 49% male; 51% female. Site A: Ethnicity: 87% Hispanic Site B: ethnicity: 40% Asian/Pacific Islander; 21% Hispanic; 15% Black; 10% White; 12% American Indian or other.	The intervention is an "indicated" drug abuse prevention program and consists of a 1 -semester class with the objective of improving academic achievement, preventing or reducing illegal drug use, and improving mood management. The intervention was offered during regular school hours and included 55 core lessons and 24 booster lessons focusing on 4 main themes: self-esteem, decision making, personal control, and interpersonal communication.	Teachers were either regular classroom teachers or school health personnel. All RY teachers completed an intensive 4-day training session, conducted by certified RY trainers.	Self-reported achievement and attendance, substance use, problem behaviors, peer affiliation patterns, and student connection to school. Academic performance variables of grade point average and truancy were obtained through school records.

[a] This study is based on an RCT, but whether or not certain schools were included was dependent on a number of criteria

[b] The total percentage of ethnicity is not 100, nevertheless these numbers are reported in the article.

Table 1. (continued)

Study/Intervention (Refs) Design	Sample	Content of intervention/model	Providers	Outcomes
Resistance skill training, normative education and both resistance skill training and normative education Hansen & Graham (1991) Cluster RCT	3011 seventh grade students of 12 junior high schools in USA. N 1-yr follow-up = 2135 (70.9%). Gender: I: 48,8 % female; R: 49.7% female; N: 55.2% female; C:55.4% female Ethnicity: -I[a]: 42,6 % Hispanic; 33,2 % White -R: 16,4 % Asian; 52,2 %White -N: 25,9 % Asian; 52,2% White -C: 17,5 % Asian; 30,5 % Hispanic; 38,8 % White	The Information only program consisted of lessons about the social and health consequences of using alcohol and other drugs. The Resistance Skills Training also gave information on the consequences of using substances. Additionally, it taught students to identify and resist peer and advertising pressure to use alcohol and other substances. The Normative Education gave information and corrected erroneous perceptions of the prevalence and acceptability of alcohol and drug use among peers and established a conservative normative school climate regarding substance use. The combined program gave information, taught resistance skills, and established conservative norms.	Programs were delivered entirely by project staff. Each had received a minimum of 2 weeks of intensive training.	Substance use and problem behavior were assessed through use of a survey.
Toward No Drug Abuse (TND) and TND network Valente et al. (2007) Cluster RCT	938 students from 14 continuation high schools in the United States. N 1-yr follow-up = 594 (63%). <u>Baseline:</u> Average age = 16,3 Average grade = 10,6 Gender: 62% male; 38 % female Ethnicity: 72% Hispanic/Latino	TND focuses on motivation, skills and decision making.. TND uses a school-based, lesson delivery model consisting of 12 lessons. Each lesson is designed to teach specific cognitive, motivational or behavioral skills that can lead to reductions in substance use. In the present study, the TND curriculum was modified to increase the number of group activities and to create small groups (three to five students) composed of their own social network members. In addition, each group was led by a peer leader chosen by their peers.	Sixteen health educators were trained by program staff to teach TND and TND Network. Peer leaders were taught how to facilitate group discussion, how to manage group interaction and encouraged to embrace anti-substance use norms. In addition, a manual was developed for health educators to use in the training.	Substance use, network size, social support and social network data were assessed through the use of surveys.

[a] I = Information only program, R = Resistance training program, N = Normative education program, C = Combined program

Table 2. Methodological quality of studies

Global Rating

Author and year	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Global rating for this study
Botvin et al. (1990)	Moderate	Weak	Weak	Moderate	Weak	Moderate	Weak
Clark et al. (2011); Ringwalt et al. (2010)	Moderate	Weak	Strong	Moderate	Weak	Strong	Weak
Ferrer-Wreder et al. (2010)	Weak	Moderate	Strong	Moderate	Weak	Moderate	Weak
Hallfors et al. (2006) ; Cho et al. (2005)	Moderate	Weak	Strong	Moderate	Strong	Strong	Moderate
Hansen & Graham (1991)	Weak	Weak	Weak	Moderate	Weak	Strong	Weak
Morgenstern et al. (2008)	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
St. Pierre et al. (2005)	Moderate	Weak	Strong	Moderate	Weak	Moderate	Weak
Valente et al. (2007)	Moderate	Weak	Strong	Moderate	Weak	Moderate	Weak

Table 3. Results of studies

Outcome	Intervention	Comparison	Iatrogenic effect
Substance use outcomes:			
– Alcohol	A cognitive-behavioral approach to substance abuse (Botvin et al., 1990)	(a) Teacher-led curriculum (b) Peer-led curriculum (c) a + booster sessions (d) b + booster sessions (e) control	The control group had significantly fewer drinkers than the teacher booster group based on the monthly and weakly measure and had a lower score on the drinking frequency index.
	Project ALERT (Clark et al., 2011)	(a) non-AYP[a]/non-ALERT (b) non-AYP/ALERT (c) AYP/non-ALERT (d) AYP/ALERT students (e) control	Students in intervention schools, whom were not making AYP, increased their 30-day alcohol use between the two posttests more than did students in the control schools (also non-AYP).
	Project ALERT (Ringwalt et al., 2010)	(a) intervention* (b) control * some teachers were trained online, others in-person	Students taught by teachers trained in person, in comparison to those being trained via an online series of lessons, for the booster lessons manifested higher 30-day alcohol use, at the time of the second posttest
	Resistance skill training, normative education and both resistance skill training and normative education (Hansen & Graham, 1991)	(a) Information only (b) Resistance skills training (c) Normative education (d) a and b (e) control	In comparison to the other programs, the Resistance Training Only program was inferior on the prevalence of 30-day alcohol use.
– Marijuana	Project ALERT (Clark et al., 2011)	(a) non-AYP[a]/non-ALERT (b) non-AYP/ALERT (c) AYP/non-ALERT (d) AYP/ALERT students (e) control	In schools that made AYP, students who received Project ALERT showed a steeper increase in lifetime marijuana use from the first to the second posttest.

[a] AYP = adequately yearly progress

Table 3. (continued)

Outcome	Intervention	Comparison	Iatrogenic effect
Substance use outcomes:			
– Marijuana	Project ALERT (Ringwalt et al., 2010)	(a) intervention* (b) control * some teachers were trained online, others in-person	Students taught by teachers trained in person for the booster lessons manifested higher lifetime marijuana use at the time of the second posttest.
	Project ALERT (St. Pierre et al., 2005)	(a) adult-led Project ALERT (b) adult-led, teen-assisted Project ALERT (c) control	Students in the teen-assisted version of the program and in the combination of both versions, showed a greater increase in the odds of past year marijuana use.
	Resistance skill training, normative education and both resistance skill training and normative education (Hansen & Graham, 1991)	(a) Information only (b) Resistance skills training (c) Normative education (d) a and b (e) control	The Information program, which was considered a placebo intervention, was more effective than the Resistance Training program in preventing the onset of marijuana use.
	Toward No Drug Abuse (TND) and TND network (Valente et al., 2007)	(a) TND (b) TND network (c) control	The interaction of peer use and being in the network condition was associated with increases in marijuana use.
– Other substances	Life Skills Training and Timewise combined (Ferrer-Wreder et al., 2010)	(a) intervention (b) control	The intervention[a] group was elevated on lifetime drug use relative to the control group.
	Project ALERT (Ringwalt et al., 2010)	(a) intervention (b) control	Students taught by teachers trained in person for the booster lessons manifested higher lifetime inhalant use as well as higher 30-day alcohol and inhalant use, at the time of the second posttest.

[a] No results were found when comparing the intervention group with the control group. However, a significant iatrogenic effect was found when the intervention was subdivided into groups according to the amount of lessons the students received.

Table 3. (continued)

Outcome	Intervention	Comparison	Iatrogenic effect
Substance use outcomes:			
– Other substances	Toward No Drug Abuse (TND) and TND network (Valente et al., 2007)	(a) TND (b) TND network (c) control	The interaction of peer use and being in the network condition was associated with increases in cocaine and composite substance use.
Mediating outcomes:			
– Attitudinal outcomes	A cognitive-behavioral approach to substance abuse (Botvin et al., 1990)	(a) Teacher-led curriculum (b) Peer-led curriculum (c) a + booster sessions (d) b + booster sessions (e) control	The teacher-led booster condition had significantly lower (more positive) drinking attitudes and marijuana use attitudes than the control condition.
	A school-based alcohol education intervention (Morgenstern et al., 2008)	(a) intervention (b) control	Compared to the control group, the intervention group had more favourable attitudes towards alcohol consumption.
	Project ALERT (St. Pierre et al., 2005)	(a) adult-led Project ALERT (b) adult-led, teen-assisted Project ALERT (c) control.	Compared to the control group, expectations of future marijuana use were higher among participants in the teen-assisted version of the program.
– Behavioral outcomes	Reconnecting Youth (Hallfors et al., 2006 ; Cho et al., 2005)	(a) Intervention (b) Control	Immediately after the intervention, the experimental group was lower on conventional peer bonding. At the 6-month follow-up, conventional peer bonding and prosocial weekend activities were lower in the experimental group. In addition, high-risk peer bonding group was higher in the experimental group at the 6-month follow-up.
	Life Skills Training and Timewise combined (Ferrer-Wreder et al., 2010)	(a) intervention (b) control	The control group reported better drug refusal skills than the intervention group.

Table 3. (continued)

Outcome	Intervention	Comparison	Iatrogenic effect
Other outcome measures	Reconnecting Youth (Hallfors et al., 2006 ; Cho et al., 2005)	(a) intervention (b) control	Immediately after the intervention, the experimental group was elevated on anger. At the 6-month follow-up, GPA and school connectedness were lower in the experimental group. In addition, anger was higher in the experimental group at the 6-month follow-up.

Figures

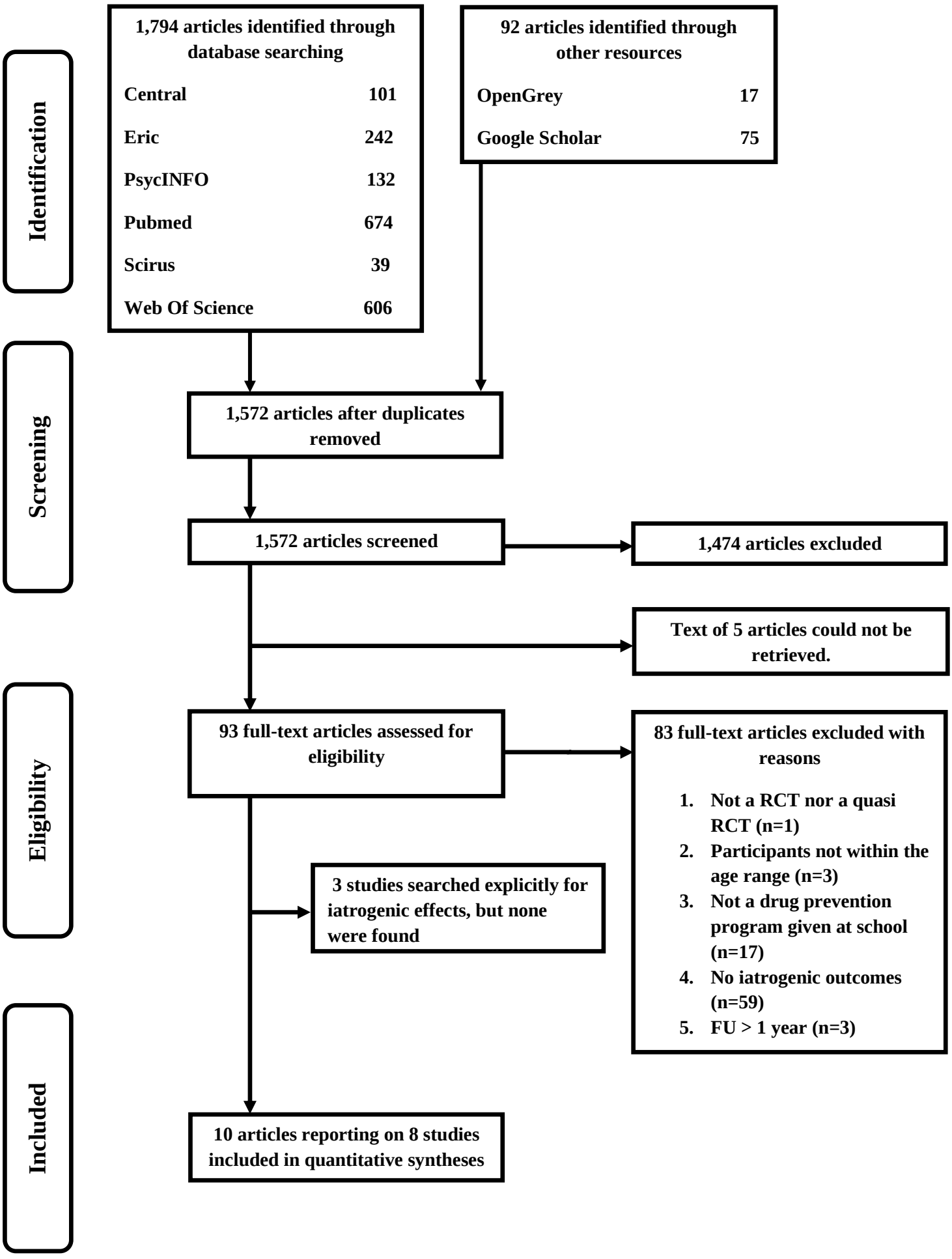

Figure 1. PRISMA flow diagram

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